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Section 5

510(K) Summary

510k Summary

Tosoh AIA-PACK RBC FOLATE

Date: **April 15, 2009**

Submitter:
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Device Name: AIA-PACK RBC FOLATE

Classification Name:
Class II
CGN
21 CFR 862.1295 Folic Acid Test System

Predicate Device: K010050, ADVIA Centaur and ACS: 180 Folate Immunoassay, Manufactured by Bayer Diagnostics Corp.

510(k) Summary

AIA-PACK RBC FOLATE

According to the requirements of 21 CFR 807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

Device Description:
The Tosoh AIA-PACK RBC FOLATE is a competitive enzyme immunoassay which, after sample hemolysis and sample pretreatment, is performed entirely within the AIA-PACK. First, sample hemolysis is performed to achieve complete hemolysis of erythrocytes and deconjugation to monoglutamate in the whole blood sample using sample hemolyzing reagents (containing ascorbic acid). After sample hemolysis, sample pretreatment is performed to release folate from endogenous binding proteins in the hemolysate sample using sample pretreatment reagents (containing sodium hydroxide and dithiothreitol).

Folate present in the pretreated test sample competes with enzyme-labeled folate for a limited number of binding sites on a fluorescein labeled bovine folate binding protein which then binds to anti-FITC (fluorescein isothiocyanate) antibody immobilized on magnetic beads. The beads are washed to remove the unbound enzyme-labeled folate and are then incubated with a fluorogenic substrate, 4-methylumbeliferyl phosphate (4MUP). The amount of enzyme labeled folate that binds to the beads is inversely proportional to the folate concentration in the test sample. A standard curve using a range of known standard concentrations is constructed and unknown folate concentrations are calculated using this curve.

The following products are required to use the Tosoh AIA-PACK RBC FOLATE.
AIA-PACK RBC FOLATE Calibrator Set.
AIA-PACK RBC FOLATE Sample Diluting Solution.
AIA-PACK RBC FOLATE Pretreatment Set.
AIA-PACK RBC FOLATE Hemolyzing Reagent Set.

Device Intended Use:
AIA-PACK RBC Folate is designed for in vitro diagnostic use only for the quantitative measurement of red blood cell folate (RBC FOLATE) in whole blood (heparin or EDTA) samples on Tosoh AIA system analyzer. Measurement of RBC Folate is used in the diagnosis and treatment of anemia.

Substantial Equivalence:

Comparison between Tosoh and Bayer –RBC Folate

Specifications	Tosoh AIA-PACK RBC FOLATE	Bayer ADVIA Centaur® FOL Lite Reagent K010050
Intended Use	In Vitro Diagnostic Use for the quantitative measurement of red blood cell folate (RBC FOLATE). Measurement of RBC Folate is used in the diagnosis and treatment of anemia.	In Vitro Diagnostic Use for the quantitative determination of folate in serum or red blood cells.
Methodology	Competitive enzyme immunoassay using fluorescence detection	Competitive immunoassay using direct chemiluminescent technology
Sample Type	Whole blood EDTA or heparin	Whole blood EDTA or heparin
Assay Components	AIA-PACK RBC FOLATE test cups, pretreatment set, hemolyzing reagent set, calibrator set, sample diluting solution	ADVIA Centaur Lite reagent pack, DTT/ Releasing Agent, FOL Ascorbic acid/Ascorbic acid diluent, FOL diluent, FOL calibrator
Solid Phase	Lyophilized magnetic beads coated with anti-FITC mouse monoclonal antibody and fluorescein labeled bovine folate binding protein and preservatives	Purified avidin bonded to paramagnetic particles in buffer with human serum albumin and preservatives
Conjugate	Alkaline phosphatase	Acridinium ester
Calibrators	6-point calibration	2-point calibration
Assay Low	0.62 ng Folate/mL (based on LOQ)	0.35 ng/mL (MDC)
Assay High	24 ng Folate/mL	24 ng/mL
Calibration Frequency	90 Days	7 Days
Time to prepare hemolysate	30 minutes	90 minutes
Incubation	40 Minutes	5 Minutes + 2.5 Minutes
Specimen Vol (Hemolysate)	160 uL	150 uL
Specimen Volume (Whole Blood)	50 uL	50 uL
Reference Range	3.4 – 10.3 ng folate/mL 148 – 531 ng RBC folate/mL	280-791 ng/mL
Hemolyzing Reagent-1 (5mL) Stability	1 day after reconstitution	30 days after reconstitution
Hemolyzing Reagent -2 (65 mL) Stability	30 days after reconstitution	Not applicable
Hemolysate Stability	5 Hours	3 Hours

	Frozen – 60 days	Frozen – 90 days
Hemolysate Multiplication Factor	22	21
Calculation Of Final Results	Manual	Automatic
Corrected Value For RBC Folate In High Serum Folate Samples	Yes	Yes

Recovery:
Recovery: Three whole blood (EDTA) samples were spiked with three different levels of RBC Folate and assayed before and after spiking.

Sample	Initial Value (ng Folate/mL)	Folate Added (ng/mL)	Expected Value (ng Folate/mL)	Measured Value (ng Folate/mL)	Expected Value (ng RBC folate/mL)	Measured Value (ng RBC folate/mL)	Percent Recovery (%)
Sample A1	4.9	5.1	10.0	10.2	487.0	500.1	102.7
	4.9	10.1	15.0	15.2	735.0	744.4	101.3
	4.9	20.3	25.2	24.6	1230.9	1205.0	97.9
Sample B1	2.0	5.3	7.2	7.2	353.6	352.8	99.8
	2.0	10.5	12.5	12.3	610.5	601.7	98.6
	2.0	21.0	23.0	22.4	1124.2	1095.4	97.4
Sample C1	5.4	5.3	10.7	10.7	520.7	521.6	100.2
	5.4	10.5	15.9	15.2	777.6	743.0	95.5
	5.4	21.0	26.4	24.9	1291.4	1216.1	94.2

Dilution: Three whole blood (EDTA) samples containing high concentrations of folate were serially diluted with AIA-PACK RBC FOLATE SAMPLE DILUTING SOLUTION and assayed.

Sample	Dilution Factor	Expected Value (ng Folate/mL)	Measured Value (ng Folate/mL)	Expected Value (ng RBC folate/mL)	Measured Value (ng RBC folate/mL)	Percent Recovery (%)
Sample A2 Hematocrit:45.0%	None	32.4	32.4	1583.7	1583.7	100.0
	7.5 /10	24.3	25.4	1187.7	1242.9	104.6
	5.0/10	16.2	17.3	791.8	844.2	106.6
	2.5/10	8.1	8.6	395.9	419.1	105.9
	1.0/10	3.2	3.2	158.4	158.4	100.0
Sample B2 Hematocrit:45.0%	None	22.5	22.5	1098.8	1098.8	100.0
	7.5 /10	16.9	17.2	824.1	840.2	102.0
	5.0/10	11.2	11.6	549.4	566.4	103.1
	2.5/10	5.6	6.4	274.7	315.2	114.7
	1.0/10	2.2	2.5	109.9	124.3	113.1
Sample C2	None	7.7	9.1	444.5	444.5	100.0

Hematocrit:37.9%	7.5 /10	5.7	7.1	333.4	348.0	104.4
	5.0/10	2.1	4.9	222.3	238.3	107.2
	2.5/10	0.5	2.6	111.1	125.1	112.5
	1.0/10	0.1	0.9	44.5	45.8	103.0

Linearity: The linearity testing for AIA-PACK RBC FOLATE was based on CLSI Protocol EP6-A. The linearity was measured on the AIA-1800, and was demonstrated to be linear from 0.5 to 40.0 ng /mL, within ±10% difference in this interval. The claimed linearity was 0.62 to 24.0 ng /mL based on discussion with the U.S. FDA.

Precision:

The precision protocol for AIA-PACK RBC FOLATE followed CLSI EP5-A2. Precision studies were conducted at one site over a period of 92 days. An AIA-1800 was used to collect the data. All data was collected on one calibration curve by one operator. The lot number of the reagent pack was G611660 and the lot number of the calibrator set was 6075 C1-C6.

2a) Within run precision was determined using three commercially available controls and one whole blood control (EDTA) in a total of 20 runs. Within each run, one set of duplicates per control was assayed. The mean of each duplicate was used to obtain the pooled standard deviation (SD), which was then used to calculate the coefficient of variation (CV).

Sample	Hematocrit (%)	Mean (ng Folate/mL)	SD (ng Folate/mL)	Mean (ng RBC folate/mL)	CV (%)
Control 1	45.0	1.90	0.112	92.8	5.9
Control 2	45.0	6.92	0.232	338.2	3.4
Control 3	45.0	23.33	0.509	1140.5	2.2
Sample A3	45.0	6.14	0.133	300.4	2.2

2b) Total precision was determined by the duplicate assay of three commercially available controls and one whole blood (EDTA) control in 20 separate runs. The means of each run were used to calculate the standard deviation (SD) and coefficient of variation (CV).

Sample	Hematocrit (%)	Mean (ng/mL)	SD (ng Folate/mL)	Mean (ng RBC folate/mL)	CV (%)
Control 1	45.0	1.90	0.155	92.8	8.2
Control 2	45.0	6.92	0.317	338.2	4.6
Control 3	45.0	23.33	0.761	1140.5	3.3
Sample A3	45.0	6.14	0.256	300.4	4.2

Correlation:

The correlation between whole blood (EDTA) and whole blood (heparin) was performed using 50 patient samples.

	After Correction for dilution factor		After correction for dilution and hematocrit	
	Deming regression	Linear Regression	Deming Regression	Linear Regression
Slope	0.959 (0.922 to 0.996)	0.951 (0.914 to 0.988)	0.955 (0.917 to 0.993)	0.946 (0.908 to 0.984)
y-Intercept	- 3.890 (-13.512 to 5.732)	- 2.133 (-11.736 to 7.469)	- 9.144 (-36.130 to 17.842)	4.068 (-30.996 to 22.860)
Correlation Coefficient	0.99		0.99	
Number of Samples (n)	50		50	
Measurement Range	34.90 to 523.37 ng folate/mL		151.59 to 1404.65 ngRBC folate/mL	

The conclusion is that whole blood (heparin) specimens were found to be substantially equivalent in performance to whole blood (EDTA) specimens.

The correlation protocol for AIA-PACK RBC FOLATE followed CLSI Protocol EP9-A2. The correlation for AIA-PACK RBC FOLATE was determined based on guidance from CLSI Protocol EP9-A2. The correlation between AIA-PACK RBC FOLATE and an alternate method was carried out using 101patient specimens.

	After Correction for dilution factor		After correction for dilution and hematocrit	
	Deming regression	Linear Regression	Deming Regression	Linear Regression
Slope	1.06 (0.950 to 1.168)	0.91 (0.805 to 1.015)	1.00 (0.897 to 1.107)	0.86 (0.761 to 0.964)
y-Intercept	-19.554 (-44.640 to 5.532)	12.22 (-11.909 to 36.353)	-26.60	58.40
Correlation Coefficient	0.87		0.86	
Number of Samples (n)	101		101	
Measurement Range	49.06 - 491.04 ng folate/mL		185 - 1333 ng RBC folate/mL	

Specificity: The following substances were tested for cross-reactivity. The cross-reactivity (%) is the percent of the compound which will be identified as RBC Folate. If these compounds are present in the specimen at the same concentration as RBC Folate, the final result will be increased by the percentages shown.

Compound	Concentration	Cross-reactivity (%)
Amethopterin	2,518 ng/mL	0.66
Leucovorin	5,231 ng/mL	0.34

Limit of Detection (LoD) and Limit of Quantitation (LoQ):

The limit of detection (LOD) and limit of quantitation (LOQ) for AIA-PACK RBC FOLATE was determined based on guidance from CLSI Protocol EP17-A. The blank sample was measured in 60 replicates. Seven low level samples were measured in 10 replicates each. The limit of detection for AIA-PACK RBC FOLATE was estimated to be 0.43 ng folate/mL. The limit of blank was 0.19 ngfolate/mL. The limit of quantitation was 0.62 ng folate/mL at 20% CV.

Standards:

Number	FDA Recognition Number	Revision	Title
C28-A2 NCCLS	7-81	June 2000	How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline - Second Edition
EP5-A2 NCCLS	7-110	8/20/04	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition
EP6-A NCCLS	7-193	4/1/03	Evaluation of the Linearity of Quantitative Measurement Procedures; A Statistical Approach; Approved Guideline
EP9-A2 NCCLS	7-92	9/20/02	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition
EP17-A NCCLS	7 - 194	10/20/04	Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

Conclusion:

The Tosoh Bioscience, Inc. AIA-PACK RBC FOLATE ASSAY is substantially equivalent to the Bayer K010050, ADVIA Centaur and ACS: 180 Folate Immunoassay for the quantitative measurement of red blood cell folate (RBC FOLATE) in whole blood (heparin or EDTA) samples on Tosoh AIA system analyzer.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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Document Mail Center – WO66-0609
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Tosoh BioScience, Inc.
c/o Ms. Judith K. Ogden
Director, New Business & Technical Development
6000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Re: k091332
Trade Name: Tosoh AIA-Pack RBC Folate
Regulation Number: 21 CFR §862.1295
Regulation Name: Folic Acid Test System.
Regulatory Class: Class II
Product Codes: CGN
Dated: September 28, 2009
Received: September 29, 2009

OCT - 2 2009

Dear Ms. Ogden:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation.(21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (301) 796-5760. For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-5680 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney C. Harper, Ph.D.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indication for Use

510(k) Number (if known): K091332

Device Name: Tosoh AIA-PACK RBC FOLATE

Indication For Use: Tosoh AIA-PACK RBC FOLATE is designed for in vitro diagnostic use only for the quantitative measurement of red blood cell folate (RBC FOLATE) in whole blood (Heparin or EDTA) samples on TOSOH AIA system analyzer. Measurement of RBC Folate is used in the diagnosis and treatment of anemia.

Prescription Use __√__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety